# SPECTINOMYCIN CHEMISTRY. II.[1]

## 9-DEOXY-4(*R*)-DIHYDROSPECTINOMYCIN AND 9-DEOXYSPECTINOMYCIN

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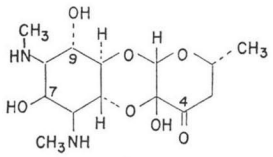
A route to 9-deoxyspectinomycin (**12**) and 9-deoxy-4(*R*)-dihydrospectinomycin (**8**) is described.

Spectinomycin (**1**) is an aminocyclitol antibiotic produced by *Streptomyces spectabilis*[2,3] which possesses a broad spectrum of activity against both Gram-positive and Gram-negative bacteria[4,5]. Its activity is reported to be bacteriostatic against *Escherichia coli* while it is rapidly bactericidal against gonococci, causing structural damage to the cytoplasmic membrane and cell lysis[6]. Spectinomycin has become increasingly important in the treatment of penicillin-resistant strains of gonorrhoeae.

Spectinomycin is an attractive substrate for chemical modification since, although its activity is generally rather low, it has many of the desirable attributes of the aminoglycosides while being devoid of the oto- and nephrotoxicities normally associated with this class of antibiotics.

It has been reported[7] that a number of natural isolates of enteric bacteria which are streptomycin-resistant are also capable of inactivating spectinomycin by R-factor-mediated adenylylation of the 9-hydroxy function. This finding prompted us to prepare 9-deoxyspectinomycin (**12**).



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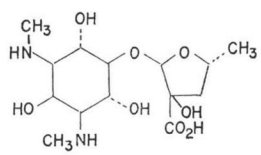

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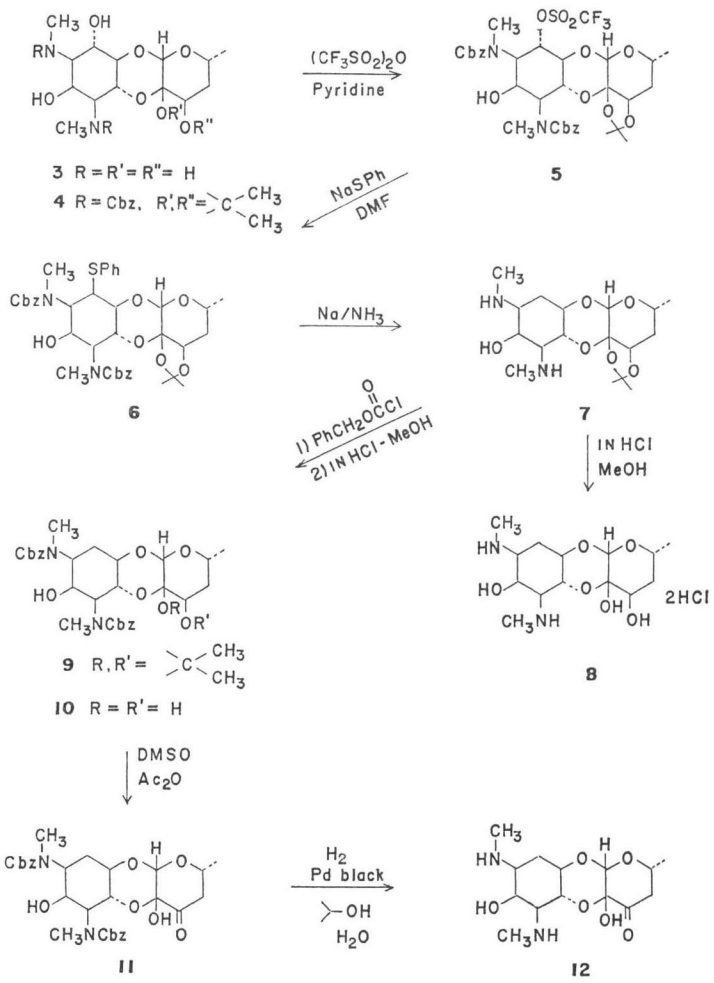
The instability of spectinomycin, which stems from the presence of the $\alpha$-keto-hemiketal functionality in the actinospectose (sugar) part, severely limits the chemistry which can successfully be carried out on this molecule. Thus, in basic solutions spectinomycin undergoes a benzylic acid type rearrangement to afford the biologically inactive $\alpha$-hydroxy acid **2**[2].

We and others[8] have circumvented this difficulty by carrying out modifications on suitably protected derivatives of 4(*R*)-dihydrospectinomycin (**3**) which are no longer capable of this mode of decomposition. Using a procedure reported by T. H. HASKELL, P. W. K. WOO and D. R. WATSON for the preparation of deoxy sugars[9], we have converted the dihydrospectinomycin(**3**) into 9-deoxy-4(*R*)-dihydrospectinomycin (**8**) and the desired 9-deoxyspectinomycin (**12**), as outlined in Scheme 1.

The quantitative conversion of *N,N'*-dicarbobenzoxy-4(*R*)-dihydrospectinomycin-4,4a-acetonide (**4**)[8b] into the monotriflate **5** was accomplished using trifluoromethanesulfonic anhydride in pyridine at $-10°C$. The equatorial C-9 hydroxy group was, as expected, much more reactive under these conditions and the 9-*O*-triflate derivative **5** was obtained exclusively. The crude triflate **5*** on reaction

* The monotriflate **5** underwent decomposition on standing and therefore was not purified but treated directly with sodium thiophenoxide.

Scheme 1.




with sodium thiophenoxide in *N,N'*-dimethylformamide(DMF) at 0°C gave 9-deoxy-9-*epi*-thiophenyl-*N,N'*-dicarbobenzoxy-4(*R*)-dihydrospectinomycin-4,4a-acetonide (**6**). The 220 MHz PMR spectrum confirmed the *epi* configuration at C-9, the small coupling between H-9 and H-9a ($J_{9,9a}=4.0$ Hz) requiring the thiophenyl group at C-9 to be axial. This configuration is the result of nucleophilic displacement without the neighboring group participation of the adjacent aminocarbobenzoxy substituent, in accord with the findings of HASKELL, *et al.*[9] Reduction of **6** with sodium in liquid ammonia afforded the acetonide **7** which on treatment with 1 N HCl in methanol gave the dihydrochloride salt of 9-deoxy-4(*R*)-dihydrospectinomycin (**8**).

Oxidation of the 9-deoxydihydrospectinomycin (**8**) required the reintroduction of amine protective groups, removable under neutral conditions. Thus, the 9-deoxy-*N,N'*-dicarbobenzoxy-4(*R*)-dihydrospectinomycin-4,4a-acetonide (**9**) was prepared by treating **7** with benzyl chloroformate in basic solution. Reaction of **9** with 1 N HCl solution in methanol afforded the required triol **10**. Of the various methods investigated, dimethylsulfoxide-acetic anhydride oxidation showed the highest degree of specificity for the C-4 hydroxyl group, yielding the 9-deoxy-*N,N'*-dicarbobenzoxyspectinomycin (**11**) from the triol **10**.

Considerable difficulty was encountered in the selective hydrogenolysis of the carbobenzoxy groups in **11**. Employing the literature conditions of either ROSENBROOK, *et al.*[8b,8c] or WILEY, *et al.*[2] resulted in the contamination of the desired deoxyspectinomycin **12** with the dihydro derivative **8**. While the hydrogenolysis was found to be complete, much faster than reported[2,8], shortening of reaction time and lowering of pressure did not improve the selectivity. However, the use of palladium black as the catalyst for hydrogenolysis in a 1 : 1 isopropanol-water mixture at atmospheric pressure proceeded cleanly to yield pure 9-deoxyspectinomycin (**12**). Further reduction of **12** to give **8** was prevented by the careful monitoring of the reaction.

Both 9-deoxy-4(*R*)-dihydrospectinomycin (**8**) and 9-deoxyspectinomycin (**12**) were found to be

inactive when tested *in vitro* against a selection of 13 spectinomycin sensitive Gram-positive and Gram-negative bacteria.

## Experimental Section

Infrared (IR) spectra were recorded on a Digilab FTS 14 spectrometer. PMR spectra measured at 100 MHz were obtained with Varian XL-100 and HA-100 instruments and 220 MHz spectra were measured on a Varian HR-220 instrument. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Mass spectra (MS) were obtained on a CEC-110 mass spectrometer.

Silica gel 60 (0.063~0.200 mm), silica gel PF-254 and plates precoated with silica gel 60 F-254 (all from E. Merck) were used for column, preparative thin-layer and thin-layer chromatography (TLC), respectively.

1,2-Dichloroethane and dimethylformamide (DMF) were dried by prolonged storage over Davidson 4A Molecular Sieves and filtered just prior to use.

Dimethylsulfoxide (DMSO) was distilled and then stored under argon over Davidson 4A Molecular Sieves. Acetic anhydride was purified by distillation and stored under an atmosphere of argon.

*N,N'*-Dicarbobenzoxy-9-*O*-[(trifluoromethyl)sulfonyl]-4(*R*)-dihydrospectinomycin-4,4a-acetonide (**5**).

A solution of *N,N'*-dicarbobenzoxy-4(*R*)-dihydrospectinomycin-4,4a-acetonide (**4**)[8b] (5.0 g, 7.78 mmole) in dry 1,2-dichloroethane (100 ml) containing dry pyridine (7.6 ml, 7.45 g, 94.1 mmole) was stirred under an argon atmosphere and cooled in an ice-ethanol bath. To this stirring, cold solution was added trifluoromethanesulfonic anhydride (1.55 ml, 2.60 g, 9.21 mmole) in dry 1,2-dichloroethane (8 ml) dropwise during a ½ hour period of time. After the addition was complete, stirring under argon in the ice-ethanol bath was continued until TLC (*n*-hexane - EtOAc, 1 : 1) indicated the reaction was complete. (1½ hours)

The yellow reaction mixture was then diluted with 200 ml of 1,2-dichloroethane and washed successively with: 150 ml of water, 150 ml of 10% HCl solution, 150 ml of saturated $NaHCO_3$ solution and 150 ml of water. Drying and concentration *in vacuo* afforded 6.43 g of a yellow foam. Further purification was not attempted because of the instability of **5**: IR (KBr) 3420, 1690, 1680 $cm^{-1}$; PMR ($CDCl_3$-$D_2O$, 100 MHz) $\delta$ 1.25 (d, 3H, C-2 $C\underline{H}_3$), 1.44 and 1.49 [2s, 6H, $C(C\underline{H}_3)_2$], 1.55~1.90 (m, 2H, *H*-3), 3.07 (broad s, 6H, N-$C\underline{H}_3$), 3.5~4.6 (m, 7H), 4.65 (s, 1H, *H*-10a), 5.14 (s, 4H, $C\underline{H}_2Ph$), 5.4~5.8 (broad m, 1H, *H*-9), 7.36 (s, 10H, arom.).

*N,N'*-Dicarbobenzoxy-9-deoxy-9-*epi*-(phenylthio)-4(*R*)-dihydrospectinomycin-4,4a-acetonide (**6**).

A suspension of sodium hydride (1.5 g of a 50% oil dispersion washed once with dry pentane, 0.75 g, 31.2 mmole) in dry DMF (20 ml) was stirred and cooled in an ice-water bath under an argon atmosphere while benzenethiol (4.0 ml, 4.28 g, 38.8 mmole) was added slowly dropwise. After the addition was complete and gas evolution had ceased, the ice bath was removed and the sodium benzenethiolate solution was allowed to stir at room temperature for 2½ hours. The resulting solution was then recooled in an ice bath, under argon, while the crude monotriflate **5** (6.37 g, 8.22 mmole) in dry DMF (15 ml) was added rapidly dropwise, while maintaining the temperature of the reaction below 5°C. After completion of the addition, stirring under argon, in the ice bath was continued for 16 hours. TLC (toluene - EtOAc, 85 : 15) showed complete disappearance of the starting triflate. To the cold, stirring reaction mixture was added 1.5 ml of glacial acetic acid in 1.5 ml of water. The resulting mixture was then diluted with toluene (350 ml) and washed four times with 100 ml of water. Drying and concentration of the toluene solution yielded 9.63 g of a foul smelling liquid.

This material was chromatographed on a silica gel column (170 g) and the product eluted with toluene - EtOAc (85 : 15). The first 470 ml of eluent contained benzenethiol. Fractions containing the product were combined and concentrated *in vacuo* to leave 5.25 g of **6** (92% of theory based on **4**) as a white foam: IR (KBr) 3360, 1692 $cm^{-1}$; PMR ($CDCl_3$-$D_2O$, 220 MHz) $\delta$ 1.27 (d, 3H, C-2 $C\underline{H}_3$), 1.45 and 1.49 [2s, 6H, $C(C\underline{H}_3)_2$], 1.60~2.05 (m, 2H, *H*-3), 2.91 and 3.13 (2s, 6H, N-$C\underline{H}_3$), 3.53 (broad

m, 1H), 3.81 (m, 2H, *H*-2 and *H*-8), 3.99 (dd, 1H, $J_{5a,6}=11$ Hz, $J_{6,7}=2.5$ Hz, *H*-6), 4.13 (m, 1H, *H*-4), 4.16 (dd, 1H, $J_{5a,9a}=9.5$ Hz, $J_{9,9a}=4$ Hz, *H*-9a), 4.51 (m, 1H, *H*-7), 4.71 (s, 1H, *H*-10a), 4.77 (dd, 1H, $J_{5a,9a}=9.5$ Hz, $J_{5a,6}=11$ Hz, *H*-5a), 5.15 (m, 4H, $C\underline{H}_2Ph$), 7.16~7.44 (m, 15H, arom.); MS *m/e* 734 ($M^+$), 719 ($M-CH_3$).

*Anal.* Calcd. for $C_{39}H_{46}N_2O_{10}S$: C, 63.74; H, 6.31; N, 3.81; S, 4.36
Found: C, 63.45; H, 6.38; N, 3.64; S, 4.19

9-Deoxy-4(*R*)-dihydrospectinomycin-4,4a-acetonide (**7**).

Into 500 ml of freshly condensed dry ammonia was placed the thiophenyl derivative **6** (3.3 g, 4.49 mmole) as a fine powder. Metallic sodium was then added to the resulting slurry with stirring until the blue color persisted for 2 minutes. Ammonium chloride was added to decompose any excess sodium and the reaction solution was allowed to warm slowly to room temperature and the ammonia to evaporate. The resulting cream-colored residue was slurried with methanol and the solid removed by filtration. The filtrate was concentrated and chromatographed on silica gel using chloroform - methanol - conc.ammonia (4.5 : 5.0 : 0.5) to give 1.4 g of pure **7**: IR (KBr) 3350, 2800 $cm^{-1}$; PMR ($CDCl_3$-$D_2O$, 100 MHz) $\delta$ 1.28 (d, 3H, C-2 $C\underline{H}_3$), 1.47 [s, 6H, $C(C\underline{H}_3)_2$], 1.50~2.20 (m, 2H, *H*-3), 2.45 (s, 6H, $NC\underline{H}_3$), 3.70~4.20 (m, 5H), 4.59 (s, 1H, *H*-10a); MS *m/e* 358 ($M^+$), 343 ($M-CH_3$), 328 ($M-HNCH_3$).

9-Deoxy-4(*R*)-dihydrospectinomycin Dihydrochloride (**8**).

The acetonide **7** (0.6 g, 1.67 mmole) was dissolved in methanol (30 ml) and 1 N HCl solution (30 ml) was added. The resulting milky white mixture was heated to reflux on a steam bath for 20 minutes. Concentration of the reaction solution gave 0.5 g of **8** as an amorphous solid: IR (KBr) 3400, 2830~2730 $cm^{-1}$; PMR ($D_2O$, 220 MHz) $\delta$ 1.78 (d, 3H, C-2 $C\underline{H}_3$), 2.30 (dt, 1H, $J_{gem}=14$ Hz, $J_{2,3eq}=3$ Hz, $J_{3eq,4}=2.5$ Hz, *H*-$3_{eq}$), 2.42 (dq, 1H, $J_{gem}=14$ Hz, $J_{2,3ax}=10.5$ Hz, $J_{3ax,4}=3$ Hz, *H*-$3_{ax}$), 2.43 (q, 1H, $J_{gem}=11.5$ Hz, $J_{9ax,9a}=12$ Hz, $J_{8,9ax}=12.5$ Hz, *H*-9ax), 2.78 (dt, 1H, $J_{gem}=11.5$ Hz, $J_{9eq,9a}=4$ Hz, $J_{8,9eq}=4.5$ Hz, *H*-9eq), 3.35 and 3.37 (2s, 6H, N-$C\underline{H}_3$), 3.99 (dd, 1H, $J_{5a,6}=10.5$ Hz, $J_{6,7}=2.5$ Hz, *H*-6), 4.02 (dq, 1H, $J_{7,8}=3$ Hz, $J_{8,9eq}=4.5$ Hz, $J_{8,9ax}=12.5$ Hz, *H*-8), 4.43 (broad t, 1H, $J_{3ax,4}=3$ Hz, $J_{3eq,4}=2.5$ Hz, *H*-4), 4.69 (dq, 1H, $J_{5a,9a}=10.5$ Hz, $J_{9eq,9a}=4$ Hz, $J_{9ax,9a}=12$ Hz, *H*-9a), 4.70 (m, 1H, *H*-2), 4.86 (t, 1H, $J_{5a,6}=J_{5a,9a}=10.5$ Hz, *H*-5a), 5.20 (broad t, 1H, $J_{6,7}=2.5$ Hz, $J_{7,8}=3$ Hz, *H*-7), 5.42 (s, 1H, *H*-10a); MS *m/e* 319 (M+1), 300 ($M-H_2O$), 288 ($M-NHCH_3$).

*Anal.* Calcd. for $C_{14}H_{26}N_2O_6\cdot 2HCl\cdot \frac{1}{2}H_2O$: C, 42.00; H, 7.30; N, 7.00
Found: C, 42.02; H, 7.21; N, 6.77

9-Deoxy-*N,N'*-dicarbobenzoxy-4(*R*)-dihydrospectinomycin-4,4a-acetonide (**9**).

The 9-deoxy-4(*R*)-dihydrospectinomycin acetonide (**7**) (2.3 g, 6.4 mmole) was dissolved in a 10% aqueous $NaHCO_3$ solution (40 ml) and cooled in an ice-water bath while benzyl chloroformate (2.2 ml, 2.63 g, 15.0 mmole) in reagent grade acetone (15 ml) was added rapidly dropwise. After the addition was complete, the resulting white mixture was vigorously stirred at room temperature for 4 hours. The acetone was then removed *in vacuo* and the aqueous mixture extracted with ethyl acetate (3× 125 ml). After drying, the combined ethyl acetate extracts were concentrated to a volume of 30 ml and petroleum ether (b.p. 30~60°C) added until no more precipitate formed. The oily solid obtained after decanting off the clear solution was purified by chromatography on silica gel (*n*-hexane - ethyl acetate, 3 : 7) to give 3.7 g of **9** as a white glass: IR (KBr) 3450~3400, 1703 $cm^{-1}$; PMR ($CDCl_3$-$D_2O$, 100 MHz) $\delta$ 1.26 (d, 3H, C-2 $C\underline{H}_3$), 1.42 and 1.46 [2s, 6H, $C(C\underline{H}_3)_2$], 1.65~2.05 (m, 4H, *H*-3 and *H*-9), 2.94 and 3.07 (2s, 6H, $NC\underline{H}_3$), 3.70~4.00 (m, 4H), 4.08 (m, 1H, *H*-4), 4.20~4.50 (m, 2H), 4.59 (s, 1H, *H*-10a), 5.10, 5.12 (2 broad s, 4H, $C\underline{H}_2Ph$), 7.32 (s, 10H, arom.); MS *m/e* 611 ($M-CH_3$), 518 ($M-HOCH_2Ph$), 491 ($M-OCOCH_2Ph$).

*Anal.* Calcd. for $C_{33}H_{42}N_2O_{10}$: C, 63.25; H, 6.76; N, 4.47
Found: C, 63.09; H, 6.69; N, 4.52

9-Deoxy-*N,N'*-dicarbobenzoxy-4(*R*)-dihydrospectinomycin (**10**).

The acetonide **9** (0.85 g, 1.36 mmole) was dissolved in methanol (40 ml) and 1 N HCl solution (40 ml) was added. The resulting milky white mixture was heated to reflux on the steam bath for 15 minutes. Removal of the methanol and water left a gum which was purified by chromatography

on silica gel ($CHCl_3$-$CH_3OH$, 9 : 1) to give 0.75 g of **10** as a white foam: IR (KBr) 3455~3410, 1685 $cm^{-1}$; PMR ($CDCl_3$-$D_2O$, 100 MHz) $\delta$ 1.21 (d, 3H, C-2 C$\underline{H}_3$), 1.60~2.50 (m, 4H, *H*-3 and *H*-9), 2.93 and 3.01 (2s, 6H, NC$\underline{H}_3$), 3.50~4.65 (m, 7H), 4.78 (s, 1H, *H*-10a), 5.11 (s, 4H, C$\underline{H}_2$Ph), 7.31 (s, 10H, arom.); MS *m/e* 544 ($M-C_3H_6$), 421 [$M-NH(CH_3)Cbz$], 128.[10]

9-Deoxy-*N,N'*-dicarbobenzoxyspectinomycin (**11**).

9-Deoxy-*N,N'*-dicarbobenzoxy-4(*R*)-dihydrospectinomycin (**10**) (0.252 g, 0.429 mmole) was dissolved in a mixture of dry DMSO (2.5 ml) and distilled acetic anhydride (1.5 ml) and stirred, under argon, at room temperature for 2 hours.* The reagents were then removed at 0.03 mm and 45°C to afford 310 mg of an oil. Traces of DMSO, acetic anhydride and starting material were removed by preparative TLC using EtOAc - hexane - acetone (50 : 50 : 15) to give 163 mg of crude product and 43 mg of recovered starting material.

Final purification of 158 mg of crude **11** was accomplished by preparative TLC using $CHCl_3$-$CH_3OH$ (95 : 5). In this way 58 mg of slightly impure **11** was obtained together with 70 mg of pure **11** as a white foam: IR (KBr) 3480~3400, 1740, 1697 $cm^{-1}$; PMR ($CDCl_3$-$D_2O$, 220 MHz) $\delta$ 1.40 (d, 3H, C-2 C$\underline{H}_3$), 1.85 (dt, 1H, $J_{gem}=11.5$ Hz, $J_{9eq,\,9a}=J_{9eq,\,8}=3.5$ Hz, *H*-9eq), 2.44 (dd, 1H, $J_{gem}=14$ Hz, $J_{3eq,\,2}=2$ Hz, *H*-3eq), 2.70~3.00 (m, 2H, *H*-3ax, *H*-9ax), 2.97 and 2.99 (2s, 6H, NC$\underline{H}_3$), 3.71 (m, 1H, *H*-2), 3.75~3.95 (m, 2H), 4.15~4.30 (m, 2H), 4.51 (broad s, 1H, *H*-7), 4.65 (s, 1H, *H*-10a), 5.14 (s, 4H, C$\underline{H}_2$Ph), 7.35 (s, 10H, arom.); MS *m/e* 584 ($M^+$), 540 ($M-CO_2$), 493 ($M-CH_2Ph$), 449 ($M-OCOCH_2Ph$).

*Anal.* Calcd. for $C_{30}H_{36}N_2O_{10}\cdot\frac{1}{2}CH_3OH$: C, 60.99; H, 6.38; N, 4.67
Found. C, 60.95; H, 6.29; N, 4.98

9-Deoxyspectinomycin (**12**).

Hydrogenolysis of the *N,N'*-dicarbobenzoxyspectinomycin (**11**) (50 mg, 0.086 mmole) in 2-propanol (7 ml) and water (7 ml) using palladium black** (25 mg) at room temperature and atmospheric pressure for 24 minutes yielded, after removal of the catalyst and concentration of the filtrate, 23.3 mg (86%) of **12** as a white glass: IR (KBr) 3400, 2800, 1740 $cm^{-1}$; PMR ($CDCl_3$-$D_2O$-DCl, 220 MHz) $\delta$ 1.78 (d, 3H, C-2 C$\underline{H}_3$), 2.25~2.40 (m, 2H, *H*-3), 2.39 (q, 1H, $J_{gem}=J_{9ax,\,9a}=J_{9ax,\,8}=11.5$ Hz, *H*-9ax), 2.72 (dt, 1H, $J_{gem}=11.5$ Hz, $J_{9eq,\,9a}=J_{9eq,\,8}=3.5$ Hz, *H*-9eq), 3.29 and 3.30 (2s, 6H, NC$\underline{H}_3$), 3.99 (dd, 1H, $J_{5a,\,6}=9.5$ Hz, $J_{6,\,7}=2.5$ Hz, *H*-6), 3.90~4.10 (m, 1H, *H*-8), 4.50 (m, 1H, *H*-2), 4.69 (dq, 1H, $J_{9ax,\,9a}=11.5$ Hz, $J_{9eq,\,9a}=3.5$ Hz, $J_{5a,\,9a}=9.5$ Hz, *H*-9a), 4.76 (t, 1H, $J_{5a,\,9a}=J_{5a,\,6}=9.5$ Hz, *H*-5a), 5.17 (broad s, 1H, *H*-7), 5.57 (s, 1H, *H*-10a); MS *m/e* 316 ($M^+$), 298 ($M-H_2O$), 285 ($M-H_2NCH_3$).

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* This oxidation was not allowed to go to completion because the additional time required resulted in the formation of side products. These side products, presumably over-oxidation products and methylthiomethyl ethers, were difficult to separate from the desired product.

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